REMARKS

Currently Claims 1-16, 18-28, 55 and 57-59 are pending and stand rejected under the Office Action mailed July 3, 2008. Claims 4-5, 9, 18, 20, 22, 24-25 and 27 are withdrawn as being directed to a non-elected species, but depend from a generic claim. In view of the above amendment and the following remarks, reconsideration is respectfully requested.

Amendments to Claims

Independent Claims 1, 28, 55 and 57 have each been amended to focus the claimed invention on the *intra*ocular administration of a solution including a mydriatic agent that is an alpha-1 adrenergic receptor agonist and an anti-inflammatory agent that is an NSAID in a liquid irrigation carrier. Independent Claim 1 calls for the alpha-1 adrenergic receptor agonist to be included in the solution at a concentration of no more than 500,000 nanomolar and for the NSAID to be included in the solution at a concentration of no more than 100,000 nanomolar. Independent Claim 28 calls for these agents to be phenylephrine and ketorolac, respectively, while independent Claim 55 calls for these agents to be either epinephrine or phenylephrine and ketorolac, respectively. Dependent claims have been cancelled or amended for consistency with the amended independent claims.

Support for the anti-inflammatory agent being an NSAID and, in Claim 28 and 55 for being ketorolac, can be found at page 12, lines 1-13. Support for the mydriatic agent being an alpha-1 adrenergic receptor agonist and, in Claims 28 and 55 for being phenylephrine or epinephrine or phenylephrine, can be found at page 13, lines 1-13, respectively. Support for the concentration of the alpha-1 adrenergic receptor agonist and the NSAID can be found at page 40, tables 20-22 and page 41, table 23, for example.

After entry of the present amendment, Claims 1, 3-5, 7-10, 12-16, 23-25, 28, 55, 57 and 59 will be pending.

OMEROS CORPORATION
1420 Fifth Avenue
Suite 2600
Seattle, Washington 98101
206.623.4688

Rejection under 35 USC § 103

Claims 1-3, 6-8, 10-16, 19, 21, 23, 26, 28, 55 and 57-59 are rejected under 35 USC § 103 based on a combination of US 5,523,316 to Gan et al. ("Gan") in view of Corbett et al., British Journal of Ophthalmology (1994) ("Corbett"), US Patent 4,474,811 to Masuda ("Masuda") and the Revision of Pharmacology (2002) ("ROP") has been presented. Applicants respectfully request reconsideration and withdrawal of this rejection.

The primary reference, Gan, discloses intraocular irrigation solutions including one or more drugs for controlling intraocular pressure in a BSS Plus® carrier solution. The drugs for controlling intraocular pressure include beta-blockers, alpha adrenergic agonists, muscarinic agonists, carbonic anhydrase inhibitors, angiostatic steroids and prostaglandins. Gan does not explicitly disclose or provide a motivation to include a mydriatic agent in an irrigation solution, instead being directed to "the provision of an improved irrigating solution which is useful in the control of intraocular pressure elevations associated with ophthalmic surgery" Gan, column 4, lines 28-32. As amended, all claims in the present application now call for the inclusion of a mydriatic agent.

The Office Action evidently recognized this distinction with respect to those claims that previously recited the inclusion of a mydriatic agent, but noted that alpha adrenergic agonists (as disclosed by Gan) also cause mydriasis. However, Gan is clearly directed to the use of alpha-2 receptor agonists to control intraocular pressure, rather than alpha-1 receptor agonist mydriatic agents claimed in the present invention. Gan states that "The alpha adrenergic agonists utilized in the present invention include all pharmaceutically acceptable compounds which are capable of controlling intraocular pressure by means of binding with alpha adrenergic receptors, particularly alpha-2 receptors." Gan, column 6, lines 5-9. This distinction has been captured in the present

OMEROS CORPORATION
1420 Fifth Avenue
Suite 2600
Seattle, Washington 98101
206.623.4688

claims by the above amendment, with all claims now requiring a mydriatic agent that is an alpha-1 adrenergic receptor agonist.

Further, not only does Gan disclose alpha-2 adrenergic receptor agonists, rather than alpha-1 adrenergic receptor agonists, Gan does not teach *combining* an alpha-1 adrenergic receptor agonist mydriatic agent with an NSAID anti-inflammatory agent, as now also claimed. Gan is directed to irrigation solutions for controlling intraocular pressure, and not to the use of solutions of *multiple* agents selected to control multiple physiologic functions associated with ophthalmologic surgery. Thus Gan would need to be modified by the secondary references cites both to replace the alpha-2 adrenergic receptor agonist with an alpha-1 adrenergic receptor agonist as a mydriatic agent and then to add an NSAID. Gan also does not disclose the low concentrations of agents recited in Claims 1, 28 and 55.

The Office Action cites Corbett for disclosing that cataract surgery is performed more easily if mydriasis can be maintained during the procedure. Corbett discloses irrigation with adrenaline (epinephrine), but again does not disclose or suggest combining the adrenaline with an NSAID as presently claimed.

Masuda is cited for teaching that a non-steroidal anti-inflammatory, "FP" (column 1, line 66), may be used intraoperatively to reduce inflammation. However, despite passing reference to intraoperative perfusion, Masuda is clearly directed to a topical "ophthalmic solution" rather than an intraocular irrigation solution, as evidenced by the teaching that preservatives may be used (Column 6, lines 1-8), which are necessary for multi-use ophthalmic drops but typically strictly avoided for intraocular administration due to toxicity concerns. Moreover, Masuda teaches the use of a preoperative topical anti-muscarinic mydriatic agent, atropine, in conjunction with the FP anti-inflammatory agent (Masuda, Test Example 4). Masuda teaches that the mydriasis effect of preoperative atropine (instilled 1.5 hours prior to paracentesis) was maintained with the

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1420 Fifth Avenue
Suite 2600
Seattle, Washington 98101
206.623.4688

installation of the FP anti-inflammatory composition. Thus Masuda discloses that intraoperative irrigation with an NSAID is sufficient to maintain operative mydriasis, teaching away from the combination of a mydriatic agent with an NSAID in an intraocular irrigation solution applied during intraocular procedures.

Finally, ROP is relied upon because of disclosing that NSAIDs can be used to inhibit miosis during cataract surgery, but this is disclosed only in the context of "topical" application of the NSAIDs. (ROP at 29). Further, for purposes of argument, if ROP is interpreted to apply to intraocular irrigation fluids, this reference would also then seem to suggest that use of an intraocular NSAID in the intraoperative irrigant would preclude the need for a mydriatic agent.

Taken separately, none of the references discloses or suggests the claimed combination of agents. When taken together as hypothetically combined in the Office Action, the references still fall short of the invention. No combination of the references recognizes that it is beneficial to both inhibit inflammation and actively maintain mydriasis during a procedure by irrigating with a solution containing both an NSAID and an alpha-1 adrenergic receptor agonist mydriatic agent applied to intraocular tissues during the trauma of the procedure, mitigating undesirable inflammation and reduction of mydriasis. Instead, one of the cited references, Masuda, actually teaches away from the claimed method of administering this combination of agents, and the another (ROP), to the extent relevant, does so as well.

Applicants again note that the rejection is based on drawing together all of the differing aspects of the presently claimed invention from a large number of references. A patent claiming several elements is not proved obvious merely by demonstrating that each of its elements was, independently, known in the art. *KSR Int'l v. Teleflex, Inc.*, 127 S. Ct. 1727, 82 USPQ2d 1385 (2007). The only road map for combining these references, which address very different aspects of ophthalmology, in this fashion is Applicants' own disclosure. This would involve the

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1420 Fifth Avenue
Suite 2600
Seattle, Washington 98101
206.623.4688

impermissible use of hindsight. *Ex Parte Crawford et al*, Appeal 20062429, Decided May 30, 2007. Further, the cited references actually teach away from the combination of the claimed invention. Applicants' respectfully submit that no *prima facie* case of obviousness has been set forth for at least this reason.

Applicants also previously presented two references, Hirowatari and Flach, that Applicants submit teach away from the present invention. While the Office Action did not find these references sufficient as teaching away from the invention (with which conclusion Applicants disagree), these references, at a minimum, clearly show that different medications cannot be routinely combined by those of skill in the art, as proposed in the Office Action, with a predictability of success. As acknowledged in the Office Action, Hirowatari teaches that repeated instillation of mydriatic and anti-inflammatory solutions may damage the corneal epithelium. While the Office Action noted that Hirowatari teaches the disclosed composition has a similar effect on mydriasis as the individual solutions, the reference clearly envisions only topical instillation to the cornea, monitoring effects on the cornea. Flach reports on a number of instances of corneal complications, including corneal melting, from topical NSAID treatment. These references exemplify that those of skill in the art would not conclude that combining the various solutions cited in the Office Action would have yielded predictable results, or that topical solutions should be applied to intraocular tissues, again illustrating that the invention is not a mere obvious combination of prior art. *KSR Int'l.*

For all of the forgoing reasons, applicants submit that no *prima facie* case of obviousness has been established, and the rejection should be withdrawn.

Nonstatutory Obviousness-Type Double Patenting Rejection

Claims 1 and 28 were rejected for nonstatutory obviousness-type double patenting based on various claims of US Patents 6,261,279, 6,413,961 and 6,420,432, all in view of Gan, Corbett,

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1420 Fifth Avenue
Suite 2600
Seattle, Washington 98101
206.623.4688

Masuda and ROP. Each of these noted US Patents was issued to inventors Demopulos et al. and assigned to the assignee of the current application. The Demopulos patents each claim perioperative methods for inhibiting pain and/or inflammation during surgical procedures, or solutions for inhibiting pain and/or inflammation, using one or a plurality of anti-inflammatory/anti-pain agents. The particular agents claimed vary for each of these patents. However, in all cases the agents claimed are anti-inflammatory and/or anti-pain agents. In no cases do the noted Demopulos patents claim the use of alpha-1 adrenergic receptor agonist mydriatic agents, alone or in combination with NSAIDs as currently claimed.

Further, the methods of the presently pending claims would not be obvious over the claims of the Demopulos patents, which are directed solely to pain and inflammation and not to promoting mydriasis as currently claimed Consideration of Gan, Corbett, Masuda and ROP do not change this outcome, because of the shortcomings of the cited references described above. Accordingly, it is respectfully submitted that present claims are not obvious over the claims of the commonly owned cited patents, alone or in view of the Gan, Corbett, Masuda and ROP references.

OMEROS CORPORATION
1420 Fifth Avenue
Suite 2600
Seattle, Washington 98101
206.623.4688

Closure

In view of the above amendment and remarks addressing the new rejection, Applicants respectfully request reconsideration and allowance of all pending claims, inclusive of Claims Claims 1, 3-5, 7-10, 12-16, 23-25, 28, 55, 57 and 59. Should the Examiner have any questions or wish to discuss any matter, he is invited to telephone the undersigned attorney.

Respectfully Submitted,

OMEROS CORPORATION

Marcia S. Kelbon
Vice President, Patent & General Counsel
Registration No. 34,358
Direct Dial No. 206.676.5020

I hereby certify that this correspondence is being deposited with the U.S. Postal Service in a sealed envelope as first class mail with postage thereon fully prepaid and addressed to Mail Stop RCE, Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450, on the below date.

9-22-09
Date

Stephanie Jansen

MSK:sj

OMEROS CORPORATION
1420 Fifth Avenue
Suite 2600
Seattle, Washington 98101
206.623.4688